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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,350	03/12/2004	Valery Krasnoperov	VASG-P01-002	2293

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EXAMINER	
AEDER, SEAN E	

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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,350	KRASNOPEROV ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-29,32-34,38-56 and 63-68* is/are pending in the application.

4a) Of the above claim(s) *38-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29,32-34 and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 11/13/07 in response to the Office Action of 7/11/07 are acknowledged and have been entered.

Claims 26-29, 32-34, 38-56, and 63-68 are pending.

Claims 38-56 have previously been withdrawn.

Claims 26-26, 32-34, and 63-68 are currently under examination.

Rejections Withdrawn

The provisional rejection, on the ground of obviousness-type double patenting, is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 26-29, 32-34, and 63-68 under 35 U.S.C. 103(a) as being unpatentable over Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15): 1-9) in view of Queen et al (US Patent 5,693,762; 12/2/97) is maintained for the reasons stated in the Office Action of 8/16/06, the Office Action of 7/11/07, and for the reasons set-forth below.

The Office Action of 7/11/07 contains the following text:

"In response to the Office Action of 8/16/06, Applicant amended claims 26, 34, 63, and 64. Further, Applicant argues that the cited references fail to provide any motivation leading the skilled artist to combine the teaching of Stephenson et al and Queen et al. Applicant further argues that Stephenson et al does not teach that inhibition of EphB4 would promote apoptosis in colon cancer cells. Applicant states that Stephenson et al does not suggest that one could use inhibitors of either Eph receptors or Ephrin as anti-cancer therapeutics. Applicant further states that Stephenson et al teaches that the role of EphB4 and other Eph receptor family members in cancer has not yet been defined. Applicant further states that the cited references fail to provide a reasonable expectation of success that antibodies to EphB4 would be effective in promoting apoptosis.

The amendments to the claims and the arguments found in the remarks filed 12/12/06 have been carefully considered, but are not deemed persuasive. In regards to the argument that the cited references fail to provide any motivation leading the skilled artist to combine the teaching of Stephenson et al and Queen et al, the Office Action of 8/16/06 states: "Stephenson et al teaches that EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Stephenson further teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular). Due to the expression pattern of EphB2 protein, one of skill in the art would recognize that antibodies against EphB2 protein would also be used in methods of diagnosing colon cancer." Further, the Office Action of 8/16/06 clearly states: "...one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific antibodies because bispecific antibodies would function as diagnostic and therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to the colon cancer cells expressing EphB4. Further, one have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled single chain antibodies because said antibodies would be more successful at targeting diagnostics and therapeutics to EphB4 expressing colon cancer cells than the entire immunoglobulin molecule taught by Stephenson et al. Further, one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled chimeric antibodies since chimeric antibodies have shown some therapeutic success. Further, one would have been motivated to isolate said human antibodies and to create radioisotope, fluorescent, enzyme, and enzyme co-factor labeled humanized antibodies because, as compared to non-recombinant mouse monoclonal antibodies and non-recombinant rabbit polyclonal antibodies, human and humanized antibodies would be more effective diagnostically and therapeutically effective because they are expected to (i) interact better with the human immune system (i.e. CDC and ADCC), (ii) reduce the HAMA response and (iii) the humanized antibodies will presumably have a longer half-life more similar to naturally occurring

human antibodies, allowing smaller and les fragment doses to be given. Further, cells and transgenic animals expressing single chain, chimeric, and humanized antibodies specific for the extracellular domain of EphB4 would be created while creating the antibodies taught by the combined teachings of Stephenson et al and Queen et al." Further, one of skill in the art would recognized that the bispecific, single-chain, chimeric, human, and humanized antibodies taught by the combined teachings of Stephenson et al and Queen et al would be monoclonal.

In regard to the arguments that Stephenson et al does not teach that inhibition of EphB4 would promote apoptosis in colon cancer cells, arguments that the prior art does not suggest that one could use inhibitors of either Eph receptors or Ephrin as anti-cancer therapeutics, arguments that the role of EphB4 and other Eph receptor family members in cancer has not yet been defined, and arguments that the cited references fail to provide a reasonable expectation of success that antibodies to EphB4 would be effective in promoting apoptosis, it is first noted that the pending claims are drawn to a product and not to a therapeutic method. Further, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation of the prior art's function, does not render the old composition patentably new to the discoverer. Atlas Powder Co. v. Ireco Inc., 190 F. 3.d 1324, 1374, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of the unknown property of inducing apoptosis, which is inherently present in the combined teachings of the prior art, does not make the pending claims patentable. In the absence of evidence to the contrary, the combined teaching of Stephenson et al and Queen would predictably produce the antibodies recited in the pending claims."

In the Reply of 11/13/07, Applicant argues that the Office has not satisfied the requirement of establishing a prima facie case of obviousness by explicitly stating articulated reasons for combining the cited references, as required by case law. Applicants state they are unable to find where in Stephenson et al it is taught that antibodies can be used as diagnostic and therapeutic agents. Applicant states that Stephenson et al fail to suggest or teach use of any antibodies as therapies, let alone antibodies against EphB4. Applicant further states that one of skill in the art would not have been motivated to make even monoclonal antibodies against EphB4 because Stephenson et al provides no suggestion or reason to do so. Applicant further states that one of skill in the art would not have been motivated to modify the polyclonal

antibodies disclosed by Stephenson et al using methods taught by Queen et al because the skilled artisan would have no reason to believe that the polyclonal antibodies of Stephenson et al could be of any therapeutic value. Applicant further states that the alleged combination of Stephenson et al and Queen et al fails to teach a monoclonal antibody against EphB4 that promotes apoptosis in a tumor cell. Applicant further states that the Examiner has not provided scientific basis supporting that monoclonal antibodies against EphB4 taught by a combination of Stephenson et al and Queen et al would inherently promote apoptosis in tumor cells. Applicant states that one of skill in the art would know that not all antibodies against EphB4 are capable of promoting apoptosis in tumor cells. Applicant further points to Example 10 of the specification to asses the ability of EphB4 antibodies to promote apoptosis in a tumor cell. Applicant further states that one of the antibodies tested (antibody #91) showed no change in apoptosis. Applicant further states that hybridoma technology is an empirical art, a skilled artisan is unable to foresee what particular antibodies will be produced, and it is logically unsound for the Examiner to assume that monoclonal antibodies against EphB4 necessarily promote apoptosis in tumor cells.

The arguments found in the Reply of 11/13/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the Office has not satisfied the requirement of establishing a prima facie case of obviousness by explicitly stating articulated reasons for combining the cited references, Stephenson et al teaches that EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Stephenson further teaches

that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular) and Stephenson et al teaches working examples demonstrating the targeting of EphB4 protein by antibodies (Figure 5, in particular). Further, due to the expression pattern of EphB4 protein, one of skill in the art would recognize that antibodies against EphB4 protein taught by the combined teachings of Stephenson et al and Queen et al would be used in methods of diagnosing colon cancer (see Figure 5, in particular) and targeting therapeutics to EphB4 protein of colon cancer cells because Stephenson et al teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular). Further, in regards to arguments that "motivation" must be explicitly articulated in the cited art, it is noted that a recent decision by the Supreme Court forecloses the argument that an explicit teaching, suggestion, or motivation is required in art to support a finding of obviousness (KSR International Co. v. Teleflex Inc., 550 U.S.-, 82 USPQ2d 1385 (2007)).

In regards to the argument that Applicant is unable to find where in Stephenson et al it is taught that antibodies can be used as a diagnostic agent, Stephenson et al teaches working examples using antibodies as a diagnostic agent for colon cancer (see Figures 4 and 5, in particular).

In regards to the argument that Applicant is unable to find where in Stephenson et al it is taught that antibodies can be used as a therapeutic agent and that Stephenson et al fail to suggest or teach use of any antibodies as therapies, Stephenson et al teaches "...therapies that target this receptor (EphB4) may find application in anti-cancer treatments" (see left column of page 2). Stephenson et al further teaches that

EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Further, using methods taught by Queen et al, one would have been motivated to create antibodies that would function as therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to colon cancer cells expressing EphB4 because said antibodies would function as therapeutic agents that target colon cancer cells.

In regards to the argument that that one of skill in the art would not have been motivated to make even monoclonal antibodies against EphB4 because Stephenson et al provides no suggestion or reason to do so, in regards to arguments that "motivation" must be explicitly articulated in the cited art, it is noted that a recent decision by the Supreme Court forecloses the argument that an explicit teaching, suggestion, or motivation is required in art to support a finding of obviousness (KSR International Co. v. Teleflex Inc., 550 U.S.-, 82 USPQ2d 1385 (2007)). Further, one would have been motivated to make monoclonal antibodies against EphB4, such as those taught on page 2760 of Inada et al (Blood, 1997, 89(8): 2757-2765), because, unlike animals used to make polyclonal antibodies, hybridomas used to make monoclonal antibodies do not require an animal facility to generate antibodies. Further, said monoclonal antibodies would be generated when producing the humanized EphB4 antibodies taught by the combined teachings of Stephenson et al and Queen et al.

In regards to the argument that one of skill in the art would not have been motivated to modify the polyclonal antibodies disclosed by Stephenson et al using

methods taught by Queen et al because the skilled artisan would have no reason to believe that the polyclonal antibodies of Stephenson et al could be of any therapeutic value, one of skill would be motivated to modify the polyclonal antibodies disclosed by Stephenson et al using the methods taught by Queen et al because Stephenson et al teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular) and Stephenson et al teaches working examples demonstrating the targeting of EphB4 protein by antibodies (Figure 5, in particular).

In regards to the argument that the alleged combination of Stephenson et al and Queen et al fails to teach a monoclonal antibody against EphB4 that promotes apoptosis in a tumor cell, monoclonal antibodies that function as therapeutics to target EphB4 colon cancer cells taught by the combined teachings of Stephenson et al and Queen et al include monoclonal antibodies comprising cytotoxic agents that function as immunotoxins to kill target cells (see discussion of immunotoxins at lines 1-24 of column 35 of Queen et al, in particular) that would promote apoptosis.

The rejection of claims 26-29, 32-34, and 63-68 as being unpatentable under 35 U.S.C. 103(a) over Inada et al (Blood, 1997, 89(8):2757-2765), in view of Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15):1-9), in further view of Queen et al (US Patent 5,693,762; 12/2/97) is maintained for the reasons stated in the Office Action of 8/16/06, the Office Action of 7/11/07, and for the reasons set-forth below.

The Office Action of 7/11/07 contains the following text:

"In response to the Office Action of 8/16/06, Applicant amended claims 26, 34, 63, and 64. Applicant further states that Inada et al does not suggest or teach any therapeutic use or potential of the EphB4 antibody. Applicant further states that absent any teaching in Inada et al that the EphB4 antibody may have any therapeutic value, one or ordinary skill would not have been motivated to modify Inada's antibodies to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4. Applicant further states that Examiner has failed to show that a skilled artisan would have predicted with a reasonable expectation of success that EphB4 antibody is capable of promoting apoptosis in a tumor cell.

The Response to the Office Action of 8/16/06 has been carefully considered, but not deemed persuasive. In regards to the argument that Inada et al does not suggest or teach any therapeutic use or potential of the EphB4 antibody, the pending claims are drawn to a product and not a method. In regards to the argument that one or ordinary skill would not have been motivated to modify Inada's antibodies to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4, one would have been motivated to modify the antibodies using methods taught by Queen et al (to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4; see previous 103 rejection) since Stephenson et al teaches that antibodies against EphB2 protein would be used in methods of diagnosing colon cancer and one of skill in the art would recognize that, from the teachings of Stephenson et al, antibodies against EphB2 protein would be useful in methods of diagnosing colon cancer.

In regards to the argument that Examiner has failed to show that a skilled artisan would have predicted with a reasonable expectation of success that EphB4 antibody is capable of promoting apoptosis in a tumor cell, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation of the prior art's function, does not render the old composition patentably new to the discoverer. Atlas Powder Co. v. Ireco Inc., 190 F. 3.d 1324, 1374, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of the unknown property of inducing apoptosis, which is inherently present in the combined teachings of the prior art, does not make the pending claims patentable. In the absence of evidence to the contrary, the combined teaching of Inada, Stephenson et al, and Queen would predictably produce the antibodies recited in the pending claims."

In the Reply of 11/13/07, Applicant argues that Inada et al does not suggest or teach any therapeutic use or potential of the EphB4 antibody that would motivate one to modify Inada's antibodies to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4. Applicant further states that Inada et al does not

teach, expressly or inherently, an isolated EphB4 antibody which promotes apoptosis in a tumor cell.

The arguments found in the Reply of 11/13/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that Inada et al does not suggest or teach any therapeutic use or potential of the EphB4 antibody, Stephenson et al teaches that EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Stephenson further teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular) and Stephenson et al teaches working examples demonstrating the targeting of EphB4 protein by antibodies (Figure 5, in particular). Further, due to the expression pattern of EphB4 protein, one of skill in the art would recognize that monoclonal antibodies against EphB4 protein taught by the combined teachings of Stephenson et al, Inada et al, and Queen et al would be used in methods of targeting therapeutics to EphB4 expressing colon cancer cells. Further, in regards to arguments that "motivation" must be explicitly articulated in the cited art, it is noted that a recent decision by the Supreme Court forecloses the argument that an explicit teaching, suggestion, or motivation is required in art to support a finding of obviousness (KSR International Co. v. Teleflex Inc., 550 U.S.-, 82 USPQ2d 1385 (2007)).

Further, in regards to the argument that Inada et al does not teach, expressly or inherently, an isolated EphB4 antibody which promotes apoptosis in a tumor cell, monoclonal antibodies that function as therapeutics to target EphB4 colon cancer cells

taught by the combined teachings of Inada et al., Stephenson et al, and Queen et al include monoclonal antibodies comprising cytotoxic agents that function as immunotoxins to kill target cells (see discussion of immunotoxins at lines 1-24 of column 35 of Queen et al, in particular) that would promote apoptosis.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

/Misook Yu/

Primary Examiner, 1642